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Boston University

Graduate School

The Reaction Between Diethylphthalate
And Various Grignard Reagents.

By

Morris Zief

(B. A., Harvard College 1937)

submitted in partial fulfillment of the
requirements for the degree of

Master of Arts

1938

John A. L. Smith

Graduate School

The Researcher's Responsibility

and Various Unethical Practices

(E. A. L. Smith, 1937)

submitted in partial fulfillment of the
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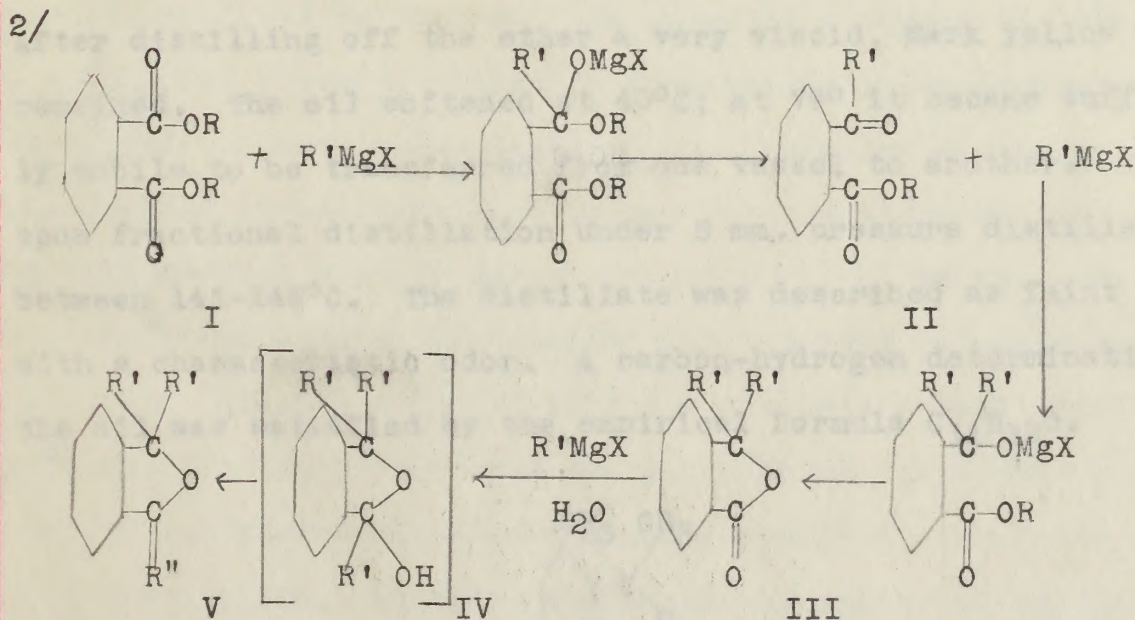
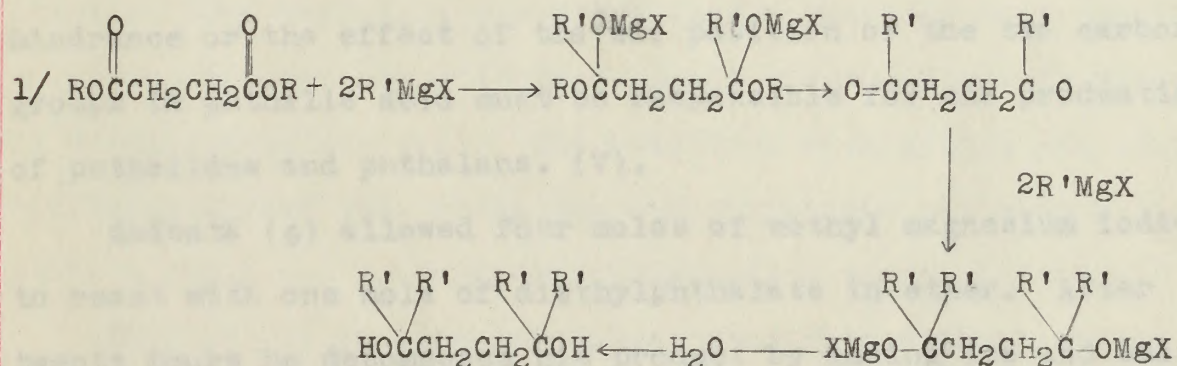
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INTRODUCTION

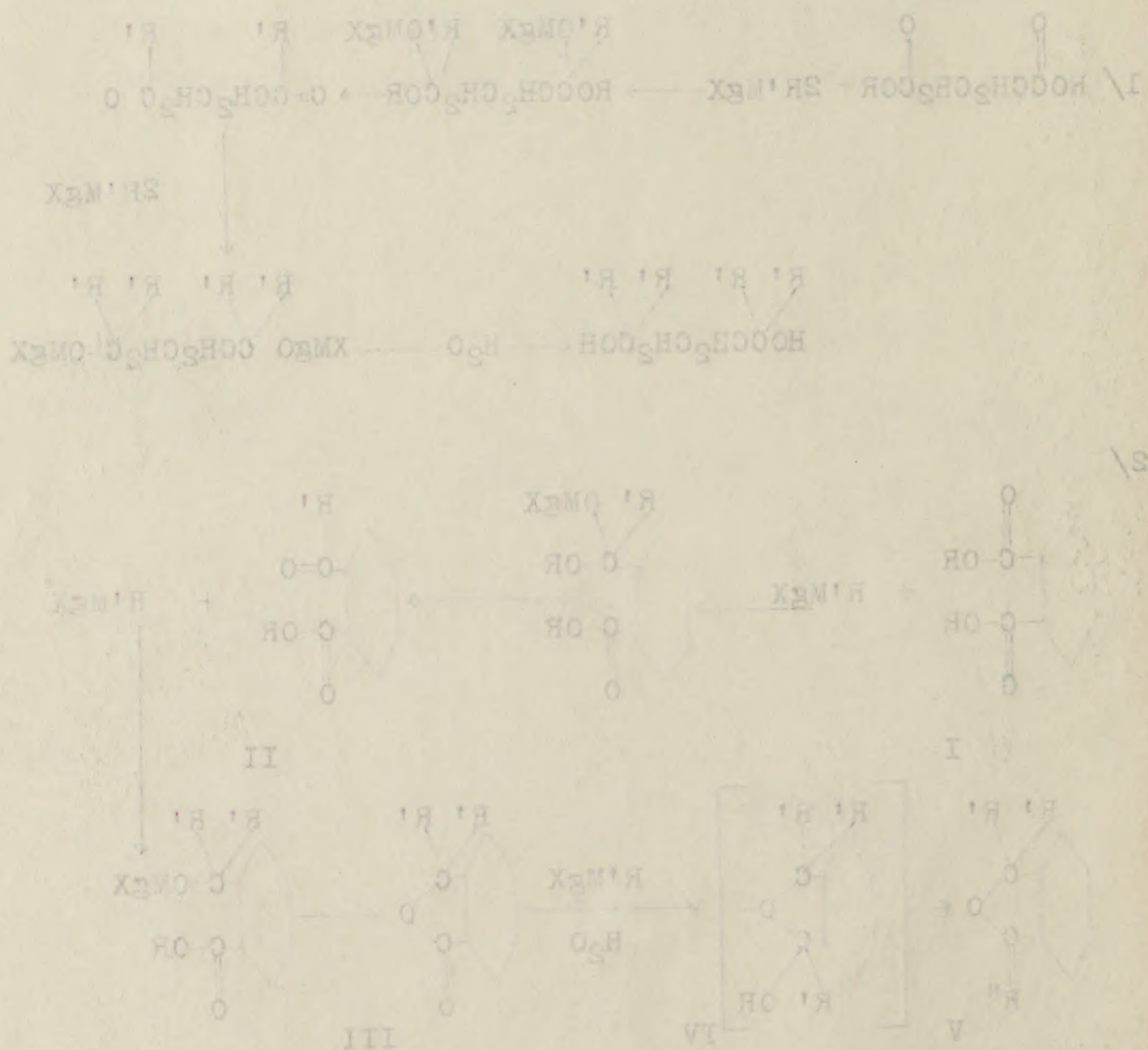
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The difference in the action of the Grignard reagent on these esters has been explained in terms of the spatial position of the carboxyl groups in succinic and phthalic acids. In suc-

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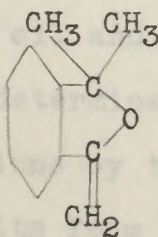
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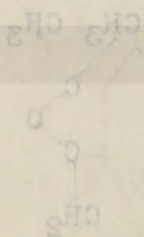
cinic acid, the two carboxyl groups are free to rotate in space. Succinic esters thus react with four molecular proportions of the Grignard reagent since the carboxyl groups when separated as much as possible have no space influence on the course of the reaction. In the case of phthalic esters only one ester group reacts with two molecular proportions of Grignard reagent. Phthalide (III) is formed as an intermediate product. Steric hindrance or the effect of the cis position of the two carboxyl groups in phthalic acid must be responsible for the production of phthalides and phthalans. (V).

Shibata (6) allowed four moles of methyl magnesium iodide to react with one mole of diethylphthalate in ether. After twenty hours he decomposed his product by adding ice and sulphuric acid. The ethereal layer was then washed well and dried. After distilling off the ether a very viscid, dark yellow oil remained. The oil softened at 40°C ; at 79° it became sufficiently mobile to be transferred from one vessel to another. The oil upon fractional distillation under 5 mm. pressure distilled between $145-146^{\circ}\text{C}$. The distillate was described as faint yellow with a characteristic odor. A carbon-hydrogen determination of the oil was satisfied by the empirical formula $\text{C}_{11}\text{H}_{12}\text{O}$.

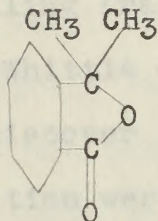


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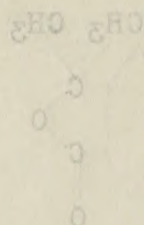
This substance was 1:1 dimethyl 3 methylenephthalan. The oil on oxidation with potassium permanganate yielded dimethylphthalide.



Shibata, upon analyzing the oil from the reaction with ethyl magnesium bromide and diethylphthalate, reported the isolation of diethylphthalide only. The reactions with methyl and ethyl halides indicate that phthalans and phthalides are produced. Shibata could not isolate the intermediate carbinol (IV).

Whittle (7) in this laboratory studied the reaction of ethylphthalate with ethyl magnesium bromide. He reproduced the results reported by Shibata. He obtained a yellow oil which was a mixture of diethylphthalide and diethylethylidenephthalan. When this oil was steam-distilled, the phthalan distilled very slowly with steam, leaving a concentrated residue of the phthalide which rapidly formed crystals (M. P. 52°C). The melting point of diethylphthalide was reported by Bauer to be 54°C (2). All tests on the oils for alcohols proved negative. Evidence for the presence of the phthalan was obtained by oxidation of the steam-distilled oil and identification of the product diethylphthalide. Whittle determined the extent of the unsaturation of different oil fractions by the use of Hanus iodine monobromide solution. His results from two samples of oil boiling at 200-205°C at a pressure of 210 mm. show unsaturation

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corresponding to mixtures of 46 and 43% of the phthalan. The results from samples of oil boiling at 210-215°C (210 mm) show unsaturation of 19 and 18% unsaturation. These results indicate that in the higher-boiling fraction the concentration of phthalide increases. Whittle determined the relative amount of unsaturation only to discover if separation of the two components by fractional distillation were possible. He concluded that diethylphthalide could not be satisfactorily isolated by this procedure. Whittle also allowed n-butyl magnesium bromide to react with diethylphthalate and obtained a light yellow oil which was oxidized by potassium permanganate. A carbon-hydrogen analysis of the crystals formed upon oxidation indicated the presence of dibutylphthalide.

Since Shibata had not reported the isolation of dimethylphthalide from his oil, an attempt to accomplish this separation by repeating part of Shibata's work was undertaken. Since the use of the Hanus determination appears to be important as a method for obtaining quantitative results, repetition of a run with n-butyl halide was completed. In order to study the reaction further, reactions of diethylphthalate with iso-butyl magnesium bromide and tertiary butyl magnesium bromide were performed. Mr. Earl Ayres (1A) repeated and extended the work with ethyl magnesium bromide.

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EXPERIMENTAL

Preparation of Materials

Methyl iodide: To 20 grams of red phosphorus 200 cc. of pure methanol was added. During the course of one hour 200 grams of finely powdered iodine was added. An efficient water condenser was connected to the flask, the mixture was left for two hours with frequent shaking and heated for two hours on the water bath under reflux. The methyl iodide was then distilled and washed successively with water, bisulphite solution, and sodium hydroxide solution. The colorless oil was distilled over a small flame. The fraction boiling at 41-43°C. was collected (1).

Isobutyl bromide: Isobutyl alcohol (150 cc.) was mixed with 340 cc. of constant boiling hydrobromic acid. The mixture was refluxed for seven hours. The top layer was separated, washed successively with ice-cold, conc. sulphuric acid, 5% sodium bicarbonate, and water. The isobutyl bromide was then dried with anhydrous calcium chloride and distilled. All that distilled between 91-94°C. was utilized (4).

Tertiary butyl chloride: In a 500 cc. separatory funnel was placed 74 grams (1 mole) of tertiary butyl alcohol and 247 cc. (3 moles) of c. p. conc. hydrochloric acid. After shaking for 20 minutes, the layers were separated. The upper layer was drawn off and washed with a 5% sodium bicarbonate solution, then with water until neutral to moist litmus paper. The chloride was dried over calcium chloride and distilled. The fraction boiling at 49.5-52°C. was collected.

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Isobutyl bromide: Isobutyl alcohol (150 cc.) was mixed with 240 cc. of constant boiling hydrobromic acid. The mixture was refluxed for seven hours. The top layer was separated, washed with anhydrous calcium chloride and distilled. All that distilled between 31-34°C. was utilized (4).

Tertiary butyl chloride: In a 500 cc. separatory funnel was placed 74 grams (1 mole) of tertiary butyl alcohol and 247 cc. (3 moles) of c. p. conc. hydrochloric acid. After shaking for 20 minutes, the layers were separated. The upper layer was drawn off and washed with a 5% sodium bicarbonate solution, then with water until neutral to moist litmus paper. The chloride was dried over calcium chloride and distilled. The fraction boiling at 49.5-52°C. was collected.

Hanus Solution: An approximately .1 N solution of sodium thiosulphate was prepared and standardized against a standard potassium dichromate solution. The standard dichromate solution was prepared by dissolving 4.9035 grams of potassium dichromate in water and diluting to a volume of one liter in a volumetric flask. Fifteen cc. of the dichromate solution was measured out by means of a burette into a 125 cc. Erlenmeyer flask, 5 cc. of conc. hydrochloric acid were added, and then 10 cc. of a 10% potassium iodide solution. The solution was diluted to about 50 cc. and titrated against the unknown thiosulphate solution. When the yellow color of the precipitated iodine had almost disappeared, 1 cc. of a 1% soluble starch solution was added and the titration was continued until the blue color of the iodine-starch complex had disappeared.

The standardized thiosulphate was next titrated against a solution of 13 grams of iodine in one liter of glacial acetic acid to which 3 grams of bromine was added. In the titration 15 cc. of IBr solution was used, 10 cc. of the 10% potassium iodide solution was added, and the solution was diluted to 50 cc. The iodine monobromide (Hanus) solution prepared in this way was calculated to be approximately .23 normal.

The n-butyl bromide was an Eastman product. The diethylphthalate which also was an Eastman product was redistilled. The entire liquid distilled between 294.5-295°C, thus indicating a reliable index of purity. Ether distilled over sodium as put out by the Baker Company was used throughout for all Grignard reactions. Before use this ether was treated with sodium and

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distilled. The magnesium turnings were kept in a desiccator for one week before use.

The Reaction Between Diethylphthalate

and Methylmagnesiumiodide

In a 500 cc. three-necked flask equipped with a mechanical stirrer, water condenser, and separatory funnel was placed 8 grams of magnesium. During the course of one hour 47.5 grams of methyl iodide (1/3 mole) dissolved in 100 cc. of ether was added dropwise. The reaction was started by first adding 3 grams of the iodide in 5 cc. of ether, heating gently, and pressing the magnesium into the liquid with a flattened stirring rod. When the reaction began, the separatory funnel was connected and the remaining ethereal solution was added. The reaction remained vigorous to the end with the formation of a dark solution. The flask was then heated on the steam bath for 1/2 hour to complete the reaction. The flask was then cooled to room temperature and 18.5 grams (1/18 mole) of diethylphthalate in 50 cc. of ether was added slowly to the Grignard reagent. The reaction was instantaneous and very vigorous, and the dark viscous addition product settled in characteristic fashion to give a yellowish upper layer and dark brown lower layer.

After 24 hours the product was hydrolyzed with 100 cc. of water containing 10 grams of sulphuric acid (5 cc.). The upper layer readily, but the bottom layer turned solid on contact with water. After the vigor of hydrolysis had passed, more water was added and the solid magnesium hydroxide in the lower layer completely dissolved. The product appeared to be in the ether layer which was reddish-brown. The water

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After 24 hours the product was hydrolyzed with 100. cc. of water containing the calculated amount of sulphuric acid (9 cc.). The upper layer hydrolyzed readily, but the bottom layer turned solid on contact with water. After the vigor of hydrolysis had passed, more water was added and the solid magnesium hydroxide in the lower layer completely dissolved. The product appeared to be in the ether layer which was reddish-brown. The water

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layer was colorless.

The ether layer was separated and washed repeatedly with water. A 5% sodium bicarbonate solution emulsified badly with the ethereal solution and took on some of the yellow color of the ethereal layer. Since Whittle reported that saturated potassium carbonate and 10% sodium hydroxide solution also emulsified badly, the excess acid was later removed only by repeated washing with water.

The ethereal layer was dried over anhydrous calcium chloride and was decanted through cotton into a Claisen flask. The ether was distilled off and the red-black tarry mass was distilled under reduced pressure. At 20 mm. pressure the first fraction was distilled between 130-160°. Fraction II, distilling between 160-166°, contained most of the product. A third fraction could not be obtained because of the violent bumping. The residue which remained consisted of more than half the volume of the original oil and charred completely. Both fractions together weighed about four grams. The product which distilled was light yellow but turned reddish over-night. A second quantity of the reddish-brown oil was prepared in the same fashion except that double the quantities of reagents were used. At 15 mm. pressure Fraction I distilling up to 130° and Fraction II, distilling from 130-180°, were collected. Fraction I consisted of 3 or 4 drops. Fraction II weighed about two grams. Above 180° the oil charred and the distillation had to be discontinued. Although the same ratio as in the first run was used, 4 moles of Grignard for 1 mole of diethyl phthalate, the yield was poorer. Obviously

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The etheral layer was dried over anhydrous calcium chloride and was decanted through cotton into a Claisen flask. The ether was distilled off and the red-black tarry mass was distilled under reduced pressure. At 80 mm. pressure the first fraction was distilled between 150-180°. Fraction II, distilling between 180-186°, contained most of the product. A third fraction could not be obtained because of the violent bumping. The residue which remained consisted of more than half the volume of the original oil and charred completely. Both fractions together weighed about four grams. The product which distilled was light yellow but turned reddish over-night. A second quantity of the reddish-brown oil was prepared in the same fashion except that double the quantities of reagents were used. At 15 mm. pressure Fraction I distilling up to 180° and Fraction II, distilling from 180-186°, were collected. Fraction I consisted of 3 or 4 drops. Fraction II weighed about two grams. Above 180° the oil charred and the distillation had to be discontinued. Although the same ratio as in the first run was used, 4 moles of Grignard for 1 mole of diethyl phthalate, the yield was poorer. Obviously

the factor of concentration must be of some importance here. Whittle performed a run, using 95 grams of methyl iodide, 24 grams magnesium, and 55 grams of diethylphthalate, exactly three times the quantity in the first run described. In his experiment no distillate appeared and the entire mass charred completely without any collectable product. Whittle ascribed the failure of the experiment entirely to the factor of concentration and disregarded the possible peculiarity of the methyl group. In view of the fact that the ratio of 4 moles Grignard reagent to 1 mole diethylphthalate, in any concentration, produced good yields of oil and very small amounts of residue with all other halides studied, this conclusion does not seem tenable.

A third quantity of the oil was prepared with the same amount of materials as in run two. A third fraction was obtained at 210-260° (20 mm.). This fraction was very viscous. When it cooled, it immediately turned into a solid gum which was inflammable. At this point no more runs with methyl iodide were attempted before comparison with other halides was possible.

Crystallization of the Oil

Crystallization of the oil varied with different oil fractions. The low-boiling fraction of the first run was light yellow and slightly viscous. The oil was allowed to stand at room temperatures for three weeks. At the end of this time large solid crystals appeared. The crystals were about one-fourth inch square and had a definite form. The high-boiling fraction of the first run was darker-colored and very viscous. Crystals sepa-

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rated overnight. From the very small low-boiling fraction of the second run one crystal separated overnight. From the higher-boiling fraction a mass of square crystals came down after cooling one-half hour. Crystallization is more rapid from the higher-boiling fractions which contain a higher percentage of dimethylphthalide (proved later by Hanus determinations).

In all the fractions the large crystals were removed from the oil with a spatula, crushed between filter paper to remove as much adhering oil as possible, then placed on a suction filter and washed carefully with ordinary ligroin. The oil dissolved much more readily than the crystals, only a small fraction of original crystalline material being lost by this method. Dimethylphthalide forms an oil so readily that no solvent suitable for recrystallization was discovered. Ordinary ligroin (partly unsaturated) was better than saturated ligroin for removing the adhering oil. Since the oil is essentially the phthalan, an unsaturated compound, the unsaturated constituents of ordinary ligroin perhaps make it a better solvent. The white crystals obtained by this procedure melted at 68.5-69.5°C. Bauer's melting point for dimethylphthalide is 68-69° (2). The striking similarity in melting point indicates that fractional distillation of the oil and careful washing of the crystals with ordinary ligroin is a satisfactory method for the isolation of pure dimethylphthalide.

Titration of Oil Fractions for Unsaturation

It was decided to determine the extent of the unsaturation

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Distillation of Oil Fractions for Unsaturation

It was decided to determine the extent of the unsaturation

of different oil fractions to learn how much separation of dimethylphthalide and phthalan was possible by distillation. The method of estimation used was the method used to determine the iodine number of unsaturated oils. The Hanus iodine monobromide solution was selected as best for the titration. The Hanus solution was prepared as previously described. The procedure used in the titration of the oils was as follows.

Approximately two-tenth gram samples of the oils were weighed out from a weighing bottle (by a dropper) into glass-stoppered reagent bottles. The samples were dissolved in 20 cc. of ligroin which had been freed from unsaturated constituents by shaking with potassium permanganate and distillation over sodium. Ligroin was used since Whittle reported that carbon tetrachloride, the usual solvent for this reaction, acted peculiarly with the oils. Exactly 25 cc. of standard iodine monobromide solution was run into each bottle. The bottles were shaken vigorously and then allowed to stand in the dark for one hour. A blank determination was run with each set of samples. After one hour the bottles were removed, the solutions were each diluted to 100 cc., 10 cc. of 10% potassium iodide was added, and the solutions were titrated with standard sodium thiosulphate with much shaking. When the end point was nearly reached, as indicated by the disappearance of the iodine color, one cc. of 1% starch solution was added. The results are given in Table I.

of different oil fractions to learn how much separation of dimethylphthalide and phthalan was possible by distillation. The method of estimation used was the method used to determine the iodine number of unsaturated oils. The Hanna iodine monobromide solution was selected as best for the titration. The Hanna solution was prepared as previously described. The procedure used in the titration of the oils was as follows.

Approximately two-tenth gram samples of the oils were weighed out from a weighing bottle (by a dropper) into glass-stoppered reagent bottles. The samples were dissolved in 20 cc. of ligroin which had been freed from unsaturated constituents by shaking with potassium permanganate and distillation over sodium. Ligroin was used since Whittle reported that carbon tetrachloride the usual solvent for this reaction, acted peculiarly with the oils. Exactly 25 cc. of standard iodine monobromide solution was run into each bottle. The bottles were shaken vigorously and then allowed to stand in the dark for one hour. A blank determination was run with each set of samples. After one hour the bottles were removed, the solutions were each diluted to 100 cc., 10 cc. of 10% potassium iodide was added, and the solutions were titrated with standard sodium thiosulfate with much shaking. When the end point was nearly reached, as indicated by the disappearance of the iodine color, one cc. of 1% starch solution was added. The results are given in Table I.

Table I

	I	IIa	IIb	IIc	IId	B
Weight of sample	.3097	.2302	.2185	.2843	.1854	
Cc. of IBr added	25.00	25.00	25.00	25.00	25.00	25.00
Cc. of thiosulphate	27.60	37.10	38.10	45.93	52.20	63.72
Cc. of IBr used for addition	14.17	10.45	10.01	6.98	4.52	
Cc. of IBr excess	10.83	14.55	14.99	18.02	20.48	
Grams phthalan	.2621	.1933	.1852	.1291	.0836	
% phthalan	84.6	83.09	84.76	45.40	45.09	
	IBr = .2317 N					
	thiosulphate = .0909 N					

I = low-boiling fraction of run I

IIa and IIb = low-boiling fraction of run II

IIc and IId = high-boiling of run II

B = blank

I eldet

g b11 c11 d11 a11 I

elqma to jnelew

delldd tEI to .00

etwqduwclnt to .00

notldbb tot baw tEI to .00

zawxe tEI to .00

delactdq ameto

delactdq *

W 0000. - etwqduwclnt

W VI08. = tEI

I put to notldswt galldod-wol - I

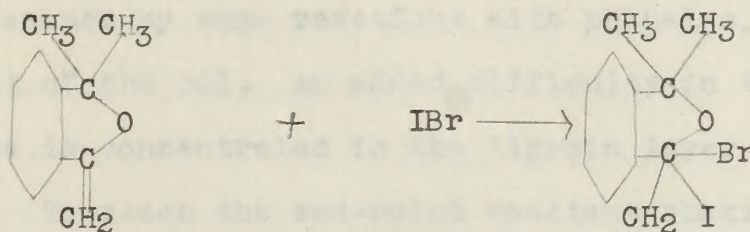
II put to notldswt galldod-wol = d11 bna a11

II put to galldod-wol = b11 bna c11

W eld = B

Sample Calculation

The unsaturated phthalan forms an addition compound with IBr solution.



One mole phthalan (160 molecular wt.) reacts with one liter of 2. N IBr solution.

$$\frac{160}{2} = \frac{X}{.2317}$$

$$X = 18.536 \text{ grams phthalan} = 1 \text{ liter } .2317 \text{ N IBr}$$

Thus .0185 grams phthalan = 1 cc. .2317 N IBr solution.

With sample I

$$27.6 \times .0909 = .2317X$$

$$X = 10.83 \text{ cc. IBr solution used in excess}$$

25.00 - 10.83 = 14.17 cc. IBr actually utilized in addition reaction.

$$14.17 \times .0185 = .2621 \text{ grams phthalan in original sample.}$$

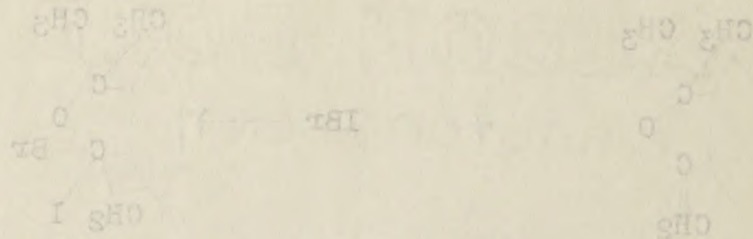
The percentage composition of the sample is based on the assumption that the oil consists entirely of phthalide and phthalan.

$$\frac{.2621}{.3097} = 84.6\% \text{ phthalan}$$

When ligroin solutions I, IIa, and IIb were shaken with IBr solution a brown precipitate separated out. This precipitate was responsible for the inability to obtain sharp end-points. No end point persisted very long. The solution always became dark after standing for ten minutes. Titration of the dark solution would

Sample Calculation

The unsaturated phthalan forms an addition compound with IBr



One mole phthalan (180 molecular wt.) reacts with one liter of 0.1 N IBr solution.

$$\frac{180}{0.1} = \frac{X}{0.009}$$

X = 16.236 grams phthalan-1 liter 0.1 N IBr

Thus, 0.188 grams phthalan-1 cc. 0.1 N IBr solution.

With sample I

$$27.6 \times 0.009 = 0.2484$$

X = 10.85 cc. IBr solution used in excess

25.00 - 10.85 = 14.15 cc. IBr actually utilized in addition

reaction.

14.15 cc. 0.188 = 2.661 grams phthalan in original sample.

The percentage composition of the sample is based on the assumption that the oil consists entirely of phthalide and phthalan.

$$\frac{2.661}{0.009} = 295.6 \text{ phthalan}$$

When IBr in solutions I, II, and III were shaken with IBr solution a brown precipitate separated out. This precipitate was responsible for the inability to obtain sharp end-points. No end point persisted very long. The solution always became dark after standing for ten minutes. Titration of the dark solution would

always cause a new end-point. The solution would again become dark-colored. No precipitate occurred with the high-boiling fractions IIc and IId. Thus the precipitate most likely must have been caused by some reactions with phthalan, the unsaturated constituent of the oil. An added difficulty in the titration is that iodine is concentrated in the ligroin layer during the titration. To reach the end-point constant shaking is necessary. If the glass stoppers are not tight leakage may result, thereby introducing an error in the calculations. The results reported here are those determined when the technique of this titration had been mastered. Previously the difference between two determinations on the same sample was 5 to 10 per cent.

Be cause the brown precipitate, which formed when the IBr solution was added to the ligroin solution, caused difficulty, solubility tests for the precipitate were determined. Dioxane was found to be a good solvent. Since the results finally obtained with ligroin checked fairly well no titrations with dioxane were performed. With the other halides studied, dioxane was substituted for ligroin. A comparison of titrations in ligroin and dioxane will be given for the n-butyl bromide run.

The results on the titrations recorded in Table I indicate that the amount of phthalan in the higher-boiling fraction is practically halved. This fact accounts for the more rapid crystallization of the phthalide from the higher fraction. To insure accurate results, samples of the oil must be weighed out as soon as the oil is obtained. Otherwise crystallization soon occurs and the true composition of the oil cannot be ascertained.

always cause a new end-point. The solution would again become dark-colored. No precipitate occurred with the high-boiling fractions IIC and IIB. Thus the precipitate most likely must have been caused by some reactions with phthalan. The unreacted constituent of the oil. An added difficulty in the titration is that iodine is concentrated in the lighter layer during the titration. To reach the end-point constant shaking is necessary. If the glass stoppers are not tight leakage may result, thereby introducing an error in the calculations. The results reported here are those determined when the technique of this titration had been mastered. Previously the difference between two determinations on the same sample was 5 to 10 per cent.

Because the brown precipitate, which formed when the IIR solution was added to the lighter solution, caused difficulty, solubility tests for the precipitate were determined. Dioxane was found to be a good solvent. Since the results finally obtained with lighter checked fairly well as titrations with dioxane were performed. With the other halides studied, dioxane was substituted for lighter. A comparison of titrations in lighter and dioxane will be given for the n-butyl bromide run.

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Oxidation of the Oil

Shibata reported the isolation of dimethylphthalide from the oil by shaking with an acid solution of potassium permanganate. Since oxidation with alkaline potassium permanganate is theoretically possible, this oxidation was attempted.

Two grams of the oil was placed in a 200 cc. round-bottom flask with 50 cc. of water, 5 grams of solid potassium permanganate, and a pellet of sodium hydroxide. A reflux condenser was attached and the material was heated to gentle boiling. The purple color of the permanganate solution persisted for two hours, then was discolored. One gram of potassium permanganate was added and the heating was continued. Soon it became necessary to filter off the manganese dioxide which caused excessived bumping. The manganese dioxide was filtered off by strong suction. The filtrate contained no oil at all and was discarded. Evidently all the oil was trapped in the residue of manganese dioxide. The manganese dioxide was extracted with ether. Upon evaporation of the ether a thick, viscous, light-colored oil remained. Since crystallization of the phthalide was known to be slow, the oil was allowed to stand at room temperature for three weeks. At the end of this period the oil was still the same with no indication of crystals formation. We may conclude from the discoloring of the potassium permanganate that the phthalan was oxidized. Most likely alkaline oxidation with the separation of phthalide crystals is possible if large quantities are used.

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enough oil was not available. The failure of the oil to crystallize is not evidence that dimethylphthalide is not formed, since dimethylphthalide forms an oil under many conditions.

Halogen Derivatives of the Oil

Whittle's procedure was followed in an attempt to prepare a bromo derivative. One gram of oil was dissolved in 20 cc. of saturated ligroin and bromine was added drop by drop to the solution. A vigorous reaction took place with the evolution of considerable heat. When the reaction ceased, the contents of the test-tube in which the reaction had been carried out consisted of a dark-red lower layer equal in bulk to the original oil, and an upper layer of ligroin colored light-red. The upper layer was poured off and allowed to evaporate. A viscous, yellow oil remained. After four additions of ether and evaporation the thick oil still persisted. No solid could be isolated. This oil did not react with alkaline permanganate.

The dark red mass in the lower layer was poured into an evaporating dish and the adhering ligroin was allowed to evaporate. The substance was successively evaporated down from ligroin solution until fumes (when breathing upon substance) were no longer present. A brownish-red, very viscous oil remained. Since Whittle had not isolated any solid from this procedure, this method was discarded.

One gram of the oil was dissolved in 15 cc. of glacial acetic acid and 3 grams of bromine were added. The mixture was allowed to stand for 15 to 30 minutes and was then poured into

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One gram of the oil was dissolved in 15 cc. of glacial acetic acid and 5 grams of bromine were added. The mixture was allowed to stand for 15 to 30 minutes and was then poured into

75 cc. of water. A yellow gum with no possibilities for a suitable derivative separated out.

The ligroin layers from four titrations with Hanus solution were combined, washed several times with water and set aside to evaporate in a current of air. In three hours the entire evaporating dish was coated with a purple layer of viscous oil which, in two weeks, became solid. The purple color indicates that the iodomonobromide addition product is very unstable, and thus useless as a derivative. The difficulty of the titrations with Hanus solution may be related to the instability of the addition compound.

Nitro Derivative:

One gram of the oil was added to 4 cc. of conc. sulphuric acid. Conc. nitric acid (4 cc.) was added drop by drop with shaking after each addition. The flask was then connected to a reflux condenser and placed in a beaker of water at 45°C for 5 minutes. The reaction mixture was then poured into 25 grams of cracked ice. A tarry product formed. Drying for two weeks in a desiccator yielded a semi-solid with no definite melting point. When fuming nitric acid was used the same product was obtained.

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The lighter layers from four titrations with Hansen solution were combined, washed several times with water and set aside to evaporate in a current of air. In three hours the entire evaporating dish was coated with a purple layer of viscous oil which, in two weeks, became solid. The purple color indicates that the monomeric addition product is very unstable, and thus useless as a derivative. The difficulty of the titrations with

Hansen solution may be related to the instability of the addition compound.

Nitric Derivative:

One gram of the oil was added to 4 cc. of conc. sulphuric acid. Conc. nitric acid (4 cc.) was added drop by drop with shaking after each addition. The flask was then connected to a reflux condenser and placed in a beaker of water at 48°C for 5 minutes. The reaction mixture was then poured into 25 grams of cracked ice. A tarry product formed. Drying for two weeks in a desiccator yielded a semi-solid with no definite melting point. When fuming nitric acid was used the same product was obtained.

Reaction Between Diethylphthalate and Butylmagnesium bromide

Normal butyl bromide (55 grams), dissolved in 100 cc. of ether, was added to magnesium (10 grams). Compared to the reaction with methyl iodide, the reaction was somewhat slower. Diethylphthalate (22 grams) in 100 cc. of ether was added very slowly. The reaction was instantaneous and vigorous throughout. The addition product was hydrolyzed and the ethereal layer was worked up as described in the reaction between diethylphthalate and methyl magnesium iodide. The final oil subjected to fractional distillation was yellow, distinctly lighter than the oil from the run with methyl magnesium iodide. The fractions at 20 mm pressure were as follows:

Fraction I ————— 160-190°

II ————— 184-190°

III ————— 195-270°

The second fraction indicated a lag in the temperature rise.

Crystallization with Dry Ice

Unlike the run with methyl magnesium iodide no crystals separated from any fraction even after one month's standing at room temperature. Solid carbon dioxide was utilized in an attempt to induce crystallization by drastic cooling. In a 400 cc. beaker, 200 cc. of ether was cooled down to -80°C by adding small pieces of CO₂ ice. Fractions I and II when cooled to -80°C showed no semblance of crystals upon continued cooling. An attempt was made to seed the various oils with a crystals of di-

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methylphthalide but no crystals formed. The oils were then dissolved in ether. At first the oils were dissolved in the least possible amount of ether. Then varying concentrations were used. The ether concentration seemed to have no effect. No crystals formed.

Since it was suggested that crystallization from a concentrated ether solution was most desirable, oil from the run with methyl magnesium iodide which had partly crystallized out was dissolved in ether along with the crystals present. When subjected to -80°C no crystals appeared. When the ether was evaporated off and cooling was attempted the crystals appeared. It would appear that crystallization results from the oil itself; seeding may be of advantage from concentrated ether solutions.

Fraction III when cooled to -80°C formed a semi-solid, yellow mass which quickly turned into the original oil at room temperature. The crystals could not be isolated because of the rapid tendency to revert to the viscous oils. The fact that a solid separated from fraction III, whereas nothing appeared in fractions I and II is in accordance with the results of the methyl run. Crystallization should be easiest from the highest-boiling fraction which contains a greater proportion of phthalide.

A comparison of the crystallization of dimethyl, diethyl, and dibutyl phthalides is interesting. Dimethylphthalide crystallizes from the oil at room temperatures within $\frac{1}{2}$ hour or three weeks, depending upon the fraction utilized. Mr. Earl Ayres (unpublished data) reports that diethylphthalide will not crystallize at all from the oil at room temperatures, no matter what

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Whittle reported the isolation of dibutylphthalide from the residue left upon fractional distillation of the oil. The crystals (M. P. 53.5°C) separated after several days. The isolation of crystals in this way could not be duplicated. Oil was prepared from four separate runs at room temperature. Fractional distillation of each oil resulted in a very dark-orange, high fraction corresponding to Whittle's fraction. No crystals separated at room temperatures or at -80°C . It would appear that specific conditions not yet clear must be necessary for crystallization.

Titration

Comparison of the titrations in ligroin and dioxane indicates that much better checks are obtained with dioxane. In every case the results from dioxane are lower than those from ligroin. In the blank runs it was noted that ligroin, like water, absorbed no IBr solution while dioxane reacted with IBr solution to a very small extent. Since the order of magnitude of this correction is about 1%, which is less than the discrepancy between checks, this correction was not made. The correction still would not account for the difference in results for both titrations. Since the

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results with dioxane obviously checked better and less difficulty was encountered at the end-point, these figures were utilized in all calculations.

The titration with dioxane differs from that with ligroin in that one phase only is involved since water and dioxane are completely miscible. The oil samples dissolved completely in 20 cc. of dioxane. When 20 cc. of IBr solution was added, the characteristic dark-brown color of IBr formed. When the solution was diluted with water, an emulsion formed. The emulsion presumably was caused by the oil and addition product being thrown out of solution by dilution with water. On the addition of thiosulphate and shaking, the solution became lighter and the addition product settled to the bottom. The first point at which a colorless solution persisted was designated the end-point. When IBr solution was added to the ligroin solution of the samples, no precipitate formed as in the case of the run with methyl magnesium iodide.

Quantitative Determination on N-Butyl Product

A quantitative estimation of phthalan and phthalide was determined from the results of Table III. The oil produced from 22 grams diethylphthalate, 10 grams magnesium, and 55 grams butyl bromide was distilled in three fractions previously described.

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Quantitative Determination on N-Butyl Product

A quantitative estimation of phthalan and phthalide was determined from the results of Table III. The oil produced from 22 grams diethylphthalate, 10 grams magnesium, and 25 grams butyl bromide was distilled in three fractions previously described.

Titration of Oil Fractions for Unsaturation

Table II

Titration with Lignoïn

	Ia	Ib	IIa	IIb	IIIA	IIIB
Weight of sample	.2988	.2370	.2066	.2008	.3249	.1951
Cc. of IBr added	20.00	20.00	20.00	20.00	20.00	20.00
Cc. of thiosulphate	22.49	24.07	23.30	24.31	25.09	28.82
Cc. of IBr used for addition	8.16	7.33	7.73	7.20	6.79	4.83
Cc. of IBr excess	11.84	12.67	12.27	12.80	13.21	15.17
Grams phthalan	.2228	.2001			.1854	.1319
% phthalan	74.56	84.43	100	100	57.06	67.61

IBr=.1911 N

thiosulphate=.1006 N

All samples were dissolved in 20 cc. lignoïn.

Ia and Ib=samples of fraction I

IIa and IIb=samples of fraction II

IIIA and IIIB=samples of fraction III

Table III
Titration with Dioxane

	Ia	Ib	IIa	IIb	IIIa	IIb
Weight of sample	.2287	.2231	.1959	.2010	.2480	.2440
Cc. of IBr added	20.00	20.00	15.00	15.00	15.00	15.00
Cc. of thiosulphate	26.01	26.49	16.72	16.65	20.74	20.83
Cc. of IBr used for addition	6.31	6.05	6.29	6.33	4.20	4.15
Cc. of IBr excess	13.69	13.95	8.71	8.67	10.80	10.85
Grams phthalan	.1723	.1652	.1717	.1728	.1147	.1133
% phthalan	75.37	72.29	87.65	85.97	46.21	46.43

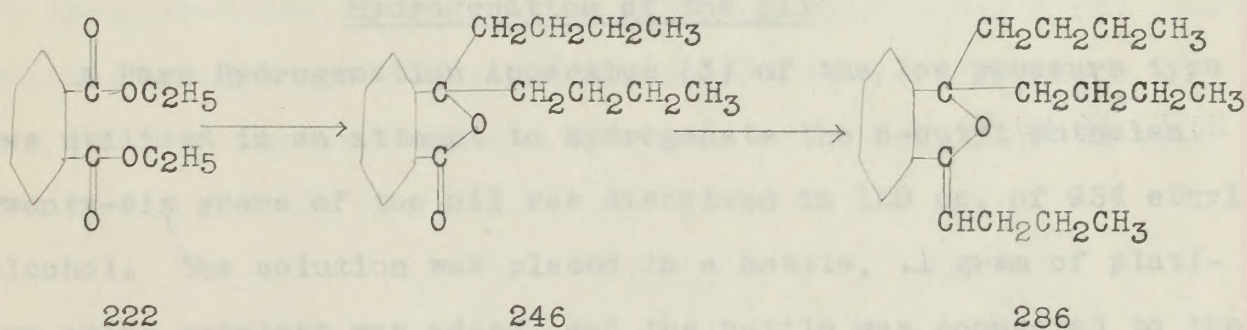
IBr = .1911 N

thiosulphate = .0995 N

Table IV

Fraction	I	II	III
Weight of oil	7.93	5.53	6.89
% phthalan	73.8	86.81	46.32
Grams phthalan	5.85	4.80	3.19
Grams phthalide	2.08	0.73	3.7

The total yield of phthalan was 13.84 grams; of phthalide 6.51 grams. The ratio of phthalan to phthalide appears to be 2 to 1.



On the assumption that all phthalan is formed from the phthalide,

$$\frac{X}{246} = \frac{13.84}{286}$$

$X = 11.9$ grams phthalide converted into phthalan.

The total quantity of phthalide formed is 18.41 grams. Calculated from the diethylphthalate used (22 grams), this corresponds to 74.84% of the theoretical yield. The 6.51 grams of phthalide in the oil indicates that 30.4% phthalide did not react further, or that 69% of the phthalide was converted into the phthalan.

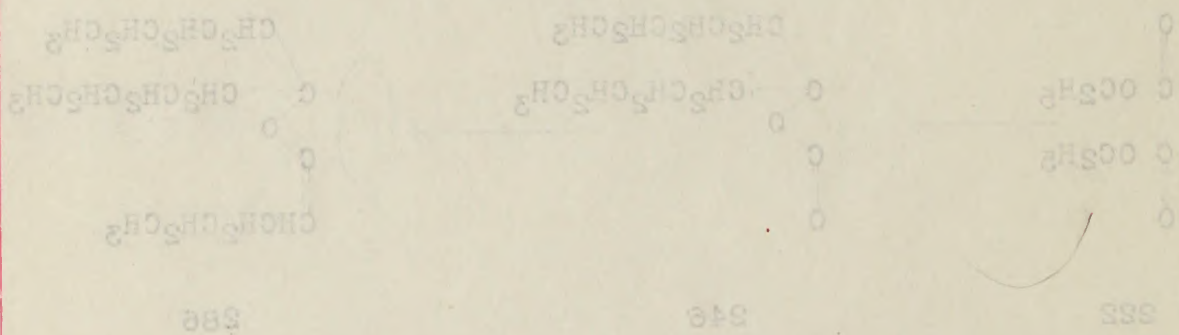
Oxidation of the Oil

Three grams of oil was refluxed with 200 cc. water and a pellet of sodium hydroxide. After adding seven grams of potassium

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Oxidation of the Oil

Three grams of oil was refluxed with 200 cc. water and a pellet of sodium hydroxide. After adding seven grams of potassium

permanganate (1 gram at a time) until the solution was faintly purple (seven hours), the oily layer remained on top apparently undiminished in volume. The oil was extracted with ether and the ether was evaporated. No solid formed. The oil gave no test with potassium permanganate. The oil, when cooled to -60°C , became a granular solid which reverted to a liquid at room temperature.

Hydrogenation of the Oil

A Parr Hydrogenation Apparatus (3) of the low pressure type was utilized in an attempt to hydrogenate the n-butyl phthalan. Twenty-six grams of the oil was dissolved in 150 cc. of 95% ethyl alcohol. The solution was placed in a bottle, .1 gram of platinum oxide catalyst was added, and the bottle was connected to the Parr Hydrogenator. The apparatus was tested for leaks and found to be satisfactory. The bottle was evacuated with an air pump and was shaken for $\frac{1}{2}$ hour at which time the reading on the gauge was steady.

	<u>Start</u>	<u>End</u>
Time	3:45	4:15
Pressure	40.9 lbs	40.6 lbs
Temperature	23.9°C	24.0°C

The apparatus was discontinued, the bottle was shaken with air, and was again evacuated. The bottle was shaken for four hours. During this time the pressure changed from 40.6 to 39 lbs. The shaking was again stopped, the bottle was removed and 1 cc.

permanganate (1 gram at a time) until the solution was faintly purple (seven hours), the oily layer remained on top apparently undiminished in volume. The oil was extracted with ether and the ether was evaporated. No solid formed. The oil gave no test with potassium permanganate. The oil, when cooled to -80°C , became a granular solid which reverted to a liquid at room temperature.

Hydrogenation of the Oil

A Parr Hydrogenation Apparatus (2) of the low pressure type was utilized in an attempt to hydrogenate the n-butyl phthalate. Twenty-six grams of the oil was dissolved in 150 cc. of 95% ethyl alcohol. The solution was placed in a bottle, 1 gram of platinum oxide catalyst was added, and the bottle was connected to the Parr Hydrogenator. The apparatus was tested for leaks and found to be satisfactory. The bottle was evacuated with an air pump and was shaken for 5 hours at which time the reading on the gauge was steady.

	<u>Start</u>	<u>End</u>
Time	3:45	4:15
Pressure	40.8 lbs	40.8 lbs
Temperature	23.9 $^{\circ}\text{C}$	24.0 $^{\circ}\text{C}$

The apparatus was discontinued, the bottle was shaken with air, and was again evacuated. The bottle was shaken for four hours. During this time the pressure changed from 40.8 to 39 lbs. The shaking was again stopped, the bottle was removed and 1 cc.

of .1 M FeSO_4 (freshly prepared) was added. This time the bottle was not evacuated when connected to the hydrogen inlet. After shaking for one hour the pressure was diminished by only one-tenth of a pound. Further shaking produced no added absorption of hydrogen. Since not enough hydrogen for a complete hydrogenation appeared to be absorbed, a change in solvent was thought worthwhile. The ethyl alcohol was distilled off and the oil was dissolved in 150 cc. of glacial acetic acid (often used in hydrogenations). The oil was only partially soluble but since shaking brought the entire oil in contact with the hydrogen atmosphere, complete solubility was not essential. The bottle was shaken for one hour.

	<u>Start</u>	<u>End</u>
Time	9:45	10:45
Pressure	43.6 lbs	42.2 lbs
Temperature	23.7°C	23.8°C

No further absorption of hydrogen occurred with repeated shaking and varied conditions at room temperature. The glacial acetic acid was extracted with ether three times, the ether residues were combined and dried over anhydrous CaCl_2 , and the ether was distilled off. An oil slightly darker than the original oil remained. This oil at 50 mm pressure distilled between 210-214°C. This narrow range was surprising since the original oil had a varied boiling range. The oil decolorized alkaline potassium permanganate, thus indicating that the unsaturated phthalan was still present. It can be concluded that hydrogenation with a platinum oxide catalyst at room temperature is slow and incomplete. No other hydrogenations were attempted.

of 1.1 M FeSO_4 (freshly prepared) was added. This time the bottle was not evacuated when connected to the hydrogen inlet. After shaking for one hour the pressure was diminished by only one-tenth of a pound. Further shaking produced no added absorption of hydrogen. Since not enough hydrogen for a complete hydrogenation appeared to be absorbed, a change in solvent was thought worthwhile. The ethyl alcohol was distilled off and the oil was dissolved in 150 cc. of glacial acetic acid (often used in hydrogenations). The oil was only partially soluble but since shaking brought the entire oil in contact with the hydrogen atmosphere, complete solubility was not essential. The bottle was shaken for one hour.

Time	Pressure	Temperature
9:45	45.8 lbs	23.7°C
10:45	45.2 lbs	23.8°C

No further absorption of hydrogen occurred with repeated shaking and varied conditions at room temperature. The glacial acetic acid was extracted with ether three times, the ether residues were combined and dried over anhydrous CaCl_2 , and the ether was distilled off. An oil slightly darker than the original oil remained. This oil at 50 mm pressure distilled between 210-215°C. This narrow range was surprising since the original oil had a varied boiling range. The oil decolorized alkaline potassium permanganate, thus indicating that the unsaturated hydrocarbon was still present. It can be concluded that hydrogenation with a platinum oxide catalyst at room temperature is slow and incomplete. No other hydrogenations were attempted.

The Reaction Between Diethylphthalate and Iso-butyl
Magnesium Bromide

To 8 grams of magnesium, 42 grams of iso-butyl bromide in 100 cc. of ether was added. To the Grignard reagent 22 grams of diethylphthalate in 100 cc. of ether was then added. In this run the ratio of halide to phthalate was decreased to three to one, the actual ratio needed. After hydrolysis and distillation of the ether, an orange oil was obtained which was distilled in three fractions (20 mm).

Fraction I--up to 185°

II-185-215°

III-215-255°

The oil from the run with n-butyl magnesium bromide had a vile odor; the iso-butyl oil had no offensive odor. No crystals formed from any fraction upon prolonged standing at room temperature or upon cooling to -80°C. The oil decolorized alkaline potassium permanganate but no crystals of the phthalide could be separated upon oxidation of the oil. The results of titrations on the oils for unsaturation are listed in Table V.

The Reaction Between Diethylphthalate and Iso-butyl

Magnesium Bromide

To 8 grams of magnesium, 42 grams of iso-butyl bromide in 100 cc. of ether was added. To the Grignard reagent 32 grams of diethylphthalate in 100 cc. of ether was then added. In this run the ratio of halide to phthalate was decreased to three to one, the actual ratio needed. After hydrolysis and distillation of the ether, an orange oil was obtained which was distilled in three fractions (20 mm.).

Fraction I-up to 185°
II-185-215°
III-215-255°

The oil from the run with n-butyl magnesium bromide had a vile odor; the iso-butyl oil had no offensive odor. No crystals formed from any fraction upon prolonged standing at room temperature or upon cooling to -80°C. The oil decolorized alkaline potassium permanganate but no crystals of the phthalide could be separated upon oxidation of the oil. The results of titrations on the oils for unsaturation are listed in Table V.

Table V

	Ia	Ib	IIa	IIb	IIIa
Weight of sample	.2085	.2047	.2026	.1904	.1446
Cc. of IBr added	15.00	15.00	15.00	15.00	15.00
Cc. of thiosulphate	25.60	25.85	26.40	26.99	28.82
Cc. of IBr used for addition	3.62	3.51	3.27	3.01	2.19
Cc. of IBr excess	11.38	11.49	11.73	11.99	12.81
Grams phthalan	.1151	11.16	.1040	.0957	.0696
% phthalan	55.20	54.53	51.33	50.27	48.13

IBr = .2223 N

thiosulphate = .0988 N

All samples were dissolved in 20 cc. of dioxane

(82)

Quantitative results, listed in Table VI, show that phthalan and phthalide were formed in almost equal quantities. We have seen in the case of the n-butyl titration that the phthalan is the predominant compound. These results are in sharp contrast to Whittle's conclusion that with higher members in the aliphatic series the predominant compound is the phthalide. Whittle performed a Hanus determination only upon the ethyl compound (49% phthalan in low fraction; 18% phthalan in the high fraction) and based his conclusion upon observation of crystal formation.

Table VI

	I		
Weight of oil	5.9	7.7	2.5
% phthalan	54.87	50.80	48.13
Grams phthalan	3.2	3.9	1.2
Grams phthalide	2.7	3.8	1.3

The total yield of phthalan was 8.3 grams; of phthalide 7.8 grams. The conversion of phthalide to phthalan involved 7.14 grams phthalide. Thus a total of 14.94 grams of phthalide were produced from 22 grams diethylphthalate, 60.73% of the theoretical yield. About 48% of the phthalide was converted to the phthalan.

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Table VI

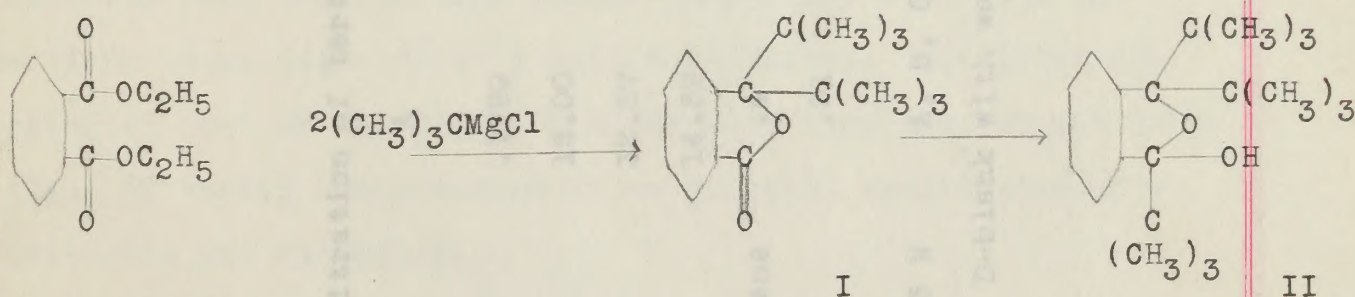
I	Weight of oil		
	Phthalan	Grams phthalan	Grams phthalide
5.9	54.87	3.2	2.7
7.7	60.80	3.9	3.3
8.5	48.13	1.2	1.3

The total yield of phthalan was 8.3 grams; of phthalide 7.8

grams. The conversion of phthalide to phthalan involved 7.14 grams phthalide. Thus a total of 14.94 grams of phthalide were produced from 22 grams diethylphthalate, 60.73% of the theoretical yield. About 45% of the phthalide was converted to the phthalan.

The Reaction of Diethylphthalate with Tertiary Butyl Chloride

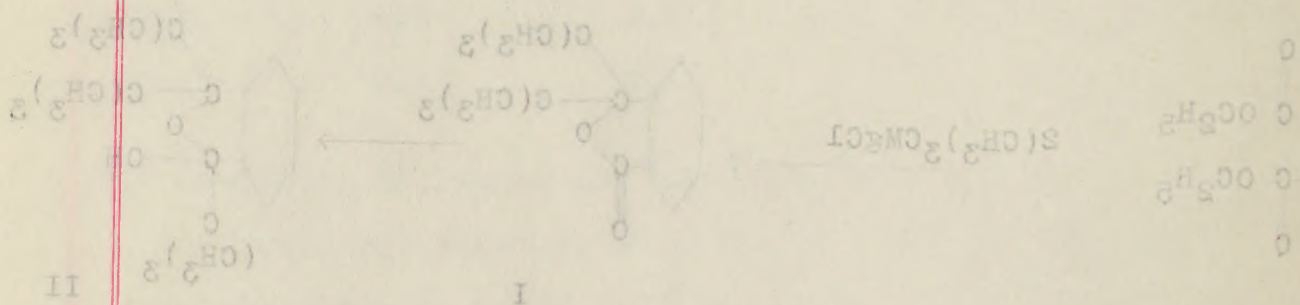
To 10 grams of magnesium, 37 grams of tertiary butyl chloride in 100 cc. of ether were added. To the Grignard reagent 22 grams of diethylphthalate in 100 cc. of ether was next added. The reaction product was worked up as previously described. An orange oil was finally obtained. This oil distilled at 300 mm practically completely at 244°C. This was the first time that any oil had distilled completely at a constant temperature. With all previous oils fractions were obtained over a wide range of temperature. The fluctuation in temperature was in accord with the belief that mixtures were present. Thus the constant boiling oil from the tertiary butyl experiment suggested the formation of one product. The reaction with tertiary butyl chloride is theoretically as follows.



The reaction reveals that the unsaturated phthalan, formed in all previous oils, is not theoretically possible. The alcohol (II) can not split off water because no available hydrogen which can combine with the OH group is present. The oil when treated with alkaline potassium permanganate gave a negative test for unsaturation. The oil added bromine very slowly. The results upon titration of the oil with Hanus solution are listed in Table VII.

The Reaction of Diethylphthalate with Tertiary Butyl Chloride

To 10 grams of magnesium, 37 grams of tertiary butyl chloride in 100 cc. of ether were added. To the Grignard reagent 22 grams of diethylphthalate in 100 cc. of ether was next added. The reaction product was worked up as previously described. An orange oil was finally obtained. This oil distilled at 300 mm pressure at 244°C. This was the first time that any oil had distilled completely at a constant temperature. With all previous oils fractions were obtained over a wide range of temperature. The fluctuation in temperature was in accord with the belief that mixtures were present. Thus the constant boiling oil from the tertiary butyl experiment suggested the formation of one product. The reaction with tertiary butyl chloride is theoretically as follows.



The reaction reveals that the unsaturated phthalan, formed in all previous oils, is not theoretically possible. The alcohol (II) can not split off water because no available hydrogen which can combine with the OH group is present. The oil when treated with alkaline potassium permanganate gave a negative test for unsaturation. The oil added bromine very slowly. The results upon distillation of the oil with Ramsay solution are listed in Table VII.

Table VII
Titration of tertiary butyl oil in dioxane

	A	B	C	D	E
Weight of sample	.1789	.1839	.1775		
Cc. of IBR added	15.00	15.00	15.00	15.00	15.00
Cc. of thiosulphate	32.37	32.15	32.48	33.75	32.85
Cc. of IBR excess	14.39	14.29	14.44		
IBR absorbed by dioxane	.4	.4	.4		
IBR used	.21	.31	.16		

IBR=.2223 N A, B, C=samples of oil Thiosulphate=.0988 N

D=blank with water E=blank with dioxane

LIV eldaz

enaxold ni lto lvgud vnaifret to noifertir

E D C B A

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87VI. 838I. 88VI.

00.8I 00.8I 00.8I 00.8I 00.8I

28.32 27.32 84.32 31.32 73.32

44.4I 43.4I 42.4I

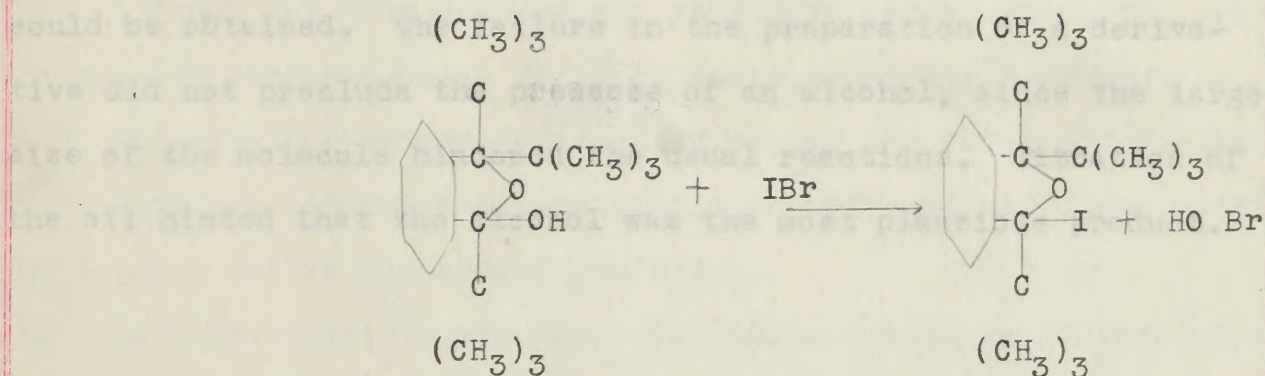
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No unsaturated product could be postulated to account for the addition of IBr solution. If the alcohol (II) is produced, the following reaction may occur.



This reaction would account for the IBr solution taken up by the oil. The titrations with the tertiary butyl oil differed from all previous titrations. When KI solution and water were added to other oils an emulsion formed; this did not occur with the tertiary butyl oil. Instead a clear solution resulted. In all preceding runs the addition product separated out; with the tertiary butyl oil a clear solution persisted. The titration resembled that of the blanks more closely than that of the other oils. To verify the presence of an alcohol, preparation of a derivative was attempted.

When one cc. of the oil was treated with sodium, a steady liberation of gas persisted. One cc. of the oil was then treated with a few drops of acetyl chloride. No liberation of heat or any apparent reaction was noted. With heating the oil became darker and the acetyl chloride off. One cc. of the oil was heated with one gram of phenylisocyanate. There was no apparent reaction. No precipitate formed on cooling. One gram of the oil was mixed with 6 cc. of 15% NaOH and 2 cc. of benzoyl chloride. After

shaking and testing for alkalinity a light-colored layer separated at the top of the solution. The substance proved to be a gum of no value as a derivative. No derivatives of typical alcohols could be obtained. The failure in the preparation of a derivative did not preclude the presence of an alcohol, since the large size of the molecule hindered the usual reactions. Titration of the oil hinted that the alcohol was the most plausible product.

With Raney iodine monohydride solution.

3) An improvement in the Raney titration utilizing dioxane as a solvent has been devised.

4) Oxidation, halogenation, nitration, hydrogenation, and crystallization of the oils are briefly summarized.

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Summary

- 1) A study has been made of the action of methyl, n-butyl, iso-butyl, and tertiary butyl Grignard reagents on diethylphthalate.
- 2) Quantitative determinations indicating the amount of dialkylphthalide and dialkyl-alkylidenephthalan produced have been made with Hanus iodine monobromide solution.
- 3) An improvement in the Hanus titration utilizing dioxane as a solvent has been devised.
- 4) Oxidation, halogenation, nitration, hydrogenation, and crystallization of the oils are briefly summarized.

Summary

- 1) A study has been made of the action of methyl, n-butyl, isobutyl, and tertiary butyl Grignard reagents on diethylphthalate.
- 2) Quantitative determinations indicating the amount of dialkylphthalide and dialkyl-alkylidene-phthalan produced have been made with Hanna iodine monobromide solution.
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- 4) Oxidation, halogenation, nitration, hydrogenation, and crystallization of the oils are briefly summarized.

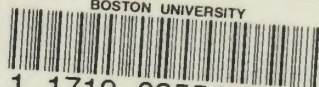
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